ESC European Society of Cardiology

Europace (2017) **0**, 1–6
doi:10.1093/europace/eux254

EP WIRE

Left atrial appendage occluder implantation in Europe: indications and anticoagulation post-implantation. Results of the European Heart Rhythm Association Survey

Roland Richard Tilz[1]*, Tatjana Potpara[2,3], Jian Chen[4,5], Dan Dobreanu[6], Torben Bjerregaard Larsen[7], Kristina Herman Haugaa[8,9], and Nikolaos Dagres[10]

[1]University Heart Center Lübeck, Medical Clinic II (Cardiology/Angiology/Intensive Care Medicine), University Hospital Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany; [2]School of Medicine, Belgrade University, Dr Subotica 8, 11000 Belgrade, Serbia; [3]Cardiology Clinic, Clinical Centre of Serbia, Visegradska 26, 11000 Belgrade, Serbia; [4]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway; [5]Department of Clinical Science, University of Bergen, 5021 Bergen, Norway; [6]Cardiology Clinic, Emergency Institute for Cardiovascular Diseases and Transplant, University of Medicine and Pharmacy, Tirgu Mures, Romania; [7]Department of Cardiology, Thrombosis and Drug Research Unit, Aarhus University Hospital, Aarhus, Denmark; [8]Department of Cardiology and Institute for Surgical Research, Center for Cardiological Innovation, Oslo University Hospital, Rikshospitalet, Sognsvannsveien 20, 0372 Oslo, Norway; [9]Institute for Clinical Medicine, University of Oslo, Oslo, Norway; and [10]Department of Electrophysiology, University Leipzig—Heart Center, Leipzig, Germany

Received 15 June 2017; editorial decision 5 July 2017; accepted 6 July 2017

The aim of this *EP Wire* survey was to assess the indications and anticoagulation strategies post-left atrial appendage occluder (LAAO) implantation for stroke prevention in patients with non-valvular atrial fibrillation in Europe. A total of 33 centres in 13 European countries completed the survey. All centres were members of the European Heart Rhythm Association Electrophysiology Research Network. Left atrial appendage occluder procedures were performed by electrophysiologists in 52% of the centres and by interventional cardiologists in the remaining centres. The *EP Wire* survey has revealed that the most common indications for LAAO are stroke prevention in patients at high thrombo-embolic risk and absolute contraindications to oral anticoagulation (OAC) therapy or a history of bleeding. Early- and long-term post-implantation anticoagulation strategies in patients with and without device thrombosis were very heterogeneous between centres with most strategies not being supported by the randomized trials. In patients without contraindications to OAC, 41% of the centres would prescribe no therapy at all after 6 months following LAAO implantation. In patients with LAA thrombus during follow-up and patients with absolute contraindications to OAC, management was highly heterogeneous and included aspirin, clopidogrel, non-vitamin K antagonist oral anticoagulants, low molecular weight heparin, surgery, unfractionated heparin, or no therapy.

Keywords Atrial fibrillation • Stroke • Anticoagulation • Bleeding • Left atrial appendage occluder • EHRA survey • EP Wire

Introduction

In patients with atrial fibrillation (AF), the left atrium is a common source for thrombo-embolic events. Approximately 90% of all thrombi identified in the left atrium can be localized in the left atrial appendage (LAA).[1] The gold standard for stroke prevention in patients with non-valvular AF and high stroke risk is oral anticoagulation (OAC) therapy with a vitamin K antagonist (VKA) or a non-VKA oral anticoagulant (NOAC). However, OAC therapy is associated with a significant bleeding risk. Percutaneous LAA occluder (LAAO) have been developed aiming at stroke prevention without the need for OAC therapy, particularly in patients with a history of bleeding on OAC therapy, high bleeding risk or contraindications to OAC therapy.[2] The purpose of this European Heart Rhythm Association (EHRA) *EP Wire* survey was to assess the indications used in the different centres, as well as the anticoagulation protocols post-LAAO implantation. It provides an update on a recently published survey regarding the indications, techniques, and outcomes of LAA closure,

* Corresponding author. Tel: 0049 1577 6097 116; fax: 00491818854435. *E-mail address:* tilz6@hotmail.com

but with special emphasis on indications and post-implantation anticoagulation strategy.[3]

Methods and results

A questionnaire was sent via the Internet to the participating centres of the EHRA Electrophysiology (EP) Research Network, which included questions on standards and policies applied by the centres and physicians regarding indications and anticoagulation protocols post-LAAO implantation.

Participating centres

Thirty-three European centres responded to this survey by completing the dedicated questionnaire. Of these, 20 (61%) were university hospitals, 7 (21%) were private hospitals, and 6 (19%) other types of hospital. One (4%) of the responding centres performed 76–100 LAA closure procedures in 2016, 3 (12%) performed 51–75 procedures, 5 (19%) performed 26–50 procedures, 14 (54%) performed 1–25 procedures, and 3 (12%) did not perform LAA closure procedures.

In 26 responding centres, the most commonly used LAAO device was the Amplatzer™ Cardiac Plug (St Jude Medical, Minneapolis, MN, USA), which was used in 70% of the centres, followed by the Watchman™ device (Boston Scientific, Maple Grove, MN, USA) which was used in 50% of the centres, and the epicardial LARIAT device (SentreHEART, Redwood, CA, USA) which was only used in one (4%) centre.

In most centres (96%), LAAO implantation was performed in an electrophysiological or coronary angiography laboratory and only in one (4%) centre in a surgical theatre. The procedure was predominantly performed under general anaesthesia in 52%, under local anaesthesia in 35%, and under deep sedation in 22% of the centres. The operator was an electrophysiologist in 52% and a cardiologist in 48% of the centres.

Indications and contraindications to left atrial appendage occluder

The majority (23 out of 26, or 88%) of the responding centres consider LAA closure in patients with AF at high thrombo-embolic risk (CHA_2DS_2-VASc ≥ 2) and absolute contraindications to OAC with either VKA or NOAC. Eighteen (69%) of the centres consider LAAO in patients with a history of bleeding on OAC (*Figure 1A*). Patients at high bleeding risk (e.g. high HAS-BLED score) were deemed to be candidates for LAAO in 11 (42%) centres. Other indications included patients with relative contraindications to OAC (27%), poor patient compliance (27%), refusal of OAC despite adequate information (19%), recurrent falls (15%), other indications (12%), or none of these (4%).

In patients with a CHA_2DS_2-VASc score ≥ 2, contraindications to LAAO included low bleeding risk (e.g. low HAS-BLED score; 50%), patients refusal of OAC despite adequate information (19%), poor compliance (8%), relative contraindications to OAC (8%), absolute contraindications to OAC (4%), none of these reasons (27%), or other (19%) (*Figure 1B*). The majority of (20 out of 23, or 88%) the responding centres offer LAAO only in selected patients, e.g. high HAS-BLED score, contraindications to OAC, but not in patients who were generally suitable for OAC. In three of the centres (13%), LAAO was offered as an alternative treatment to OAC even in patients suitable for OAC therapy.

Left atrial appendage imaging

The question regarding LAA imaging prior to LAAO implant was answered by 23 centres: 16 (74%) performed transoesophageal echocardiography (TEE), 4 (17%) TEE and computed tomography (CT) or magnetic resonance imaging (MRI), and 3 (9%) only CT or MRI without TEE. During LAAO implantation, 91% (20 out of 22) of the responding centres use TEE guidance and 9% (2 out of 22) used intracardiac echocardiography.

Anticoagulation protocol in the initial phase (0–6 months) following left atrial appendage occluder

Patients without contraindications to OAC and no LAA leak during follow-up TEE

Following LAAO, 12 out of 22 (55%) centres prescribed dual antiplatelet therapy (DAT) for a limited period (e.g. up to 6 weeks–6 months), followed by a single antiplatelet agent. Five centres (23%) prescribed OAC for 6 weeks and DAT for 6 months. Two centres (9%) prescribed OAC and antiplatelet therapy (DAT) for a limited period (e.g. up to 6 weeks–6 months), followed by antiplatelet monotherapy, two centres (9%) used NOAC therapy only for a limited period (e.g. up to 6 weeks–6 months), and two other centres (9%) used antiplatelet monotherapy. One centre (5%) prescribed OAC monotherapy for a limited period (e.g. up to 6 weeks–6 months), followed by antiplatelet monotherapy, and another centre (5%) prescribed aspirin for 6 months only.

Patients with absolute contraindications to OAC and no LAA leak during follow-up TEE

In this patients population, the OAC strategy was very heterogeneous between centres. Following LAAO, 14 out of 22 (64%) centres prescribe DAT for a limited period (e.g. up to 6 weeks–6 months), followed by antiplatelet therapy. Three centres (14%) used antiplatelet monotherapy and two centres (9%) administered low molecular weight heparin therapy only. Five centres (23%) prescribed OAC for 6 weeks and DAT for 6 months. Two centres (9%) prescribed OAC and DAT for a limited period (e.g. up to 6 weeks–6 months), followed by antiplatelet monotherapy, two centres (9%) used NOAC therapy only for a limited period (e.g. up to 6 weeks–6 months), and two other centres (9%) used antiplatelet monotherapy. One centre (5%) prescribed OAC monotherapy for a limited period (e.g. up to 6 weeks–6 months), followed by antiplatelet monotherapy and another centre (4%) prescribed aspirin for 6 months only. Five centres used individual protocols: one centre prescribed OAC for 6 weeks and DAT for 6 months, one centre used OAC and antiplatelet therapy for a limited period (e.g. up to 6 weeks–6 months), followed by antiplatelet monotherapy, one centre prescribed NOAC only for a limited period (e.g. up to 6 weeks–6 months), one centre used aspirin for 6 months, and one centre did not prescribe any drug at all.

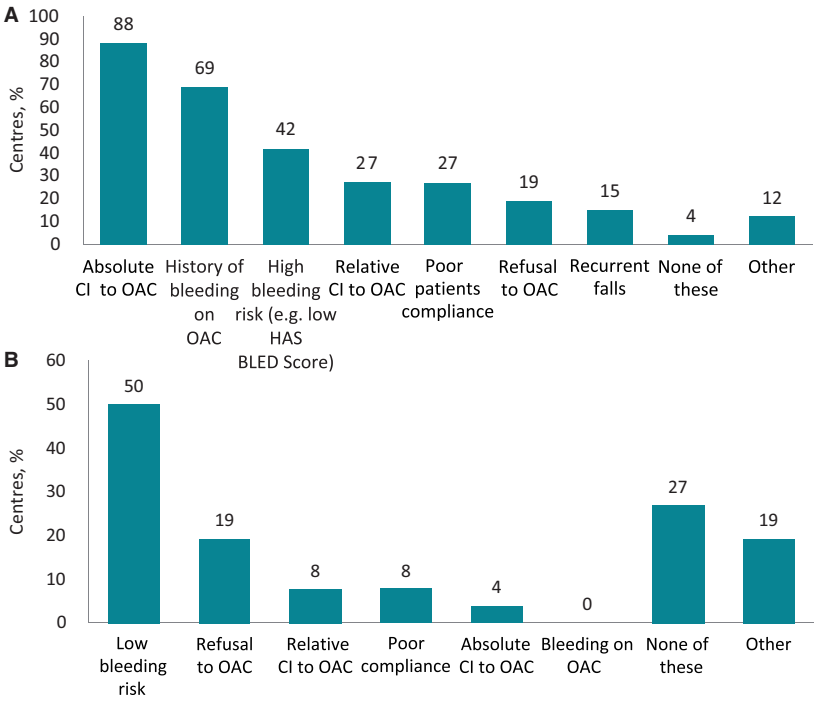

Figure 1 In patients with atrial fibrillation and a CHA_2DS_2-VASc score ≥2, indications for LAAO (A) and contraindications for LAAO (B) at your institutions are (multiple answers). "Other" included thrombus in the left atrial appendage (n=1), contraindications for general anaesthesia (n=1) and other reasons. LAAO, left atrial appendage occluder; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation.

Anticoagulation protocol in the long-term phase (>6 months) following left atrial appendage occluder implantation

Patients without contraindications to VKA or NOAC and no LAA leak during follow-up TEE

In these patients, the most common strategy was aspirin monotherapy (59%), followed by no therapy at all (41%), clopidogrel (14%), and NOAC (9%) (*Figure 2A*).

Patients with absolute contraindications to VKA or NOAC and no LAA leak during follow-up TEE

The majority of the responding centres (52%) prescribed no therapy, 43% prescribed aspirin and 5% clopidogrel.

Patients with absolute contraindications to VKA or NOAC and LAA leak 2–5 mm during follow-up TEE

In this patient population, 43% (9 out of 21) of the responding centres prescribed aspirin only, 33% recommended no therapy, 24% clopidogrel and 5% NOAC therapy.

Patients with absolute contraindications to VKA or NOAC and LAA leak > 5 mm during follow-up TEE

The strategy was as follows: aspirin in 38%, clopidogrel in 33%, no therapy in 24%, NOAC in 5%, surgical closure in 5%, vitamin K antagonist in 5%, and other strategies in 5% (*Figure 2B*).

Patients with absolute contraindications to VKA or NOAC and device thrombus during follow-up TEE

In these patients, the strategy was as follows: low molecular weight heparin in 43%, OAC in 29%, clopidogrel in 19%, aspirin in 14%, surgery in 10%, no therapy in 10%, unfractionated heparin in 5%, and other strategy in 5% (*Figure 2C*).

Reasons for not implanting or limiting the implantation of left atrial appendage occluder

In 57% (12 out of 21) of the responding centres, limited efficacy data compared with OAC were the predominant reasons for limiting or not implanting LAAO. Other reasons include the procedural risk (stroke, tamponade, etc., 38%), comorbidity (33%), costs (e.g. price or reimbursement issues; 24%) and operator availability (too difficult procedure; 10%).

Discussion

In this survey we provide insights to the indications for LAAO implantation for stroke prevention in patients with non-valvular AF and the anticoagulation strategies post-implantation.[2,4]

The vast majority of the responding centres performed LAAO implantation. All centres implanted less than 100 devices annually, with more than 50% of implanting centres performing less or equal to 25 procedures annually. This is particularly of interest, since several

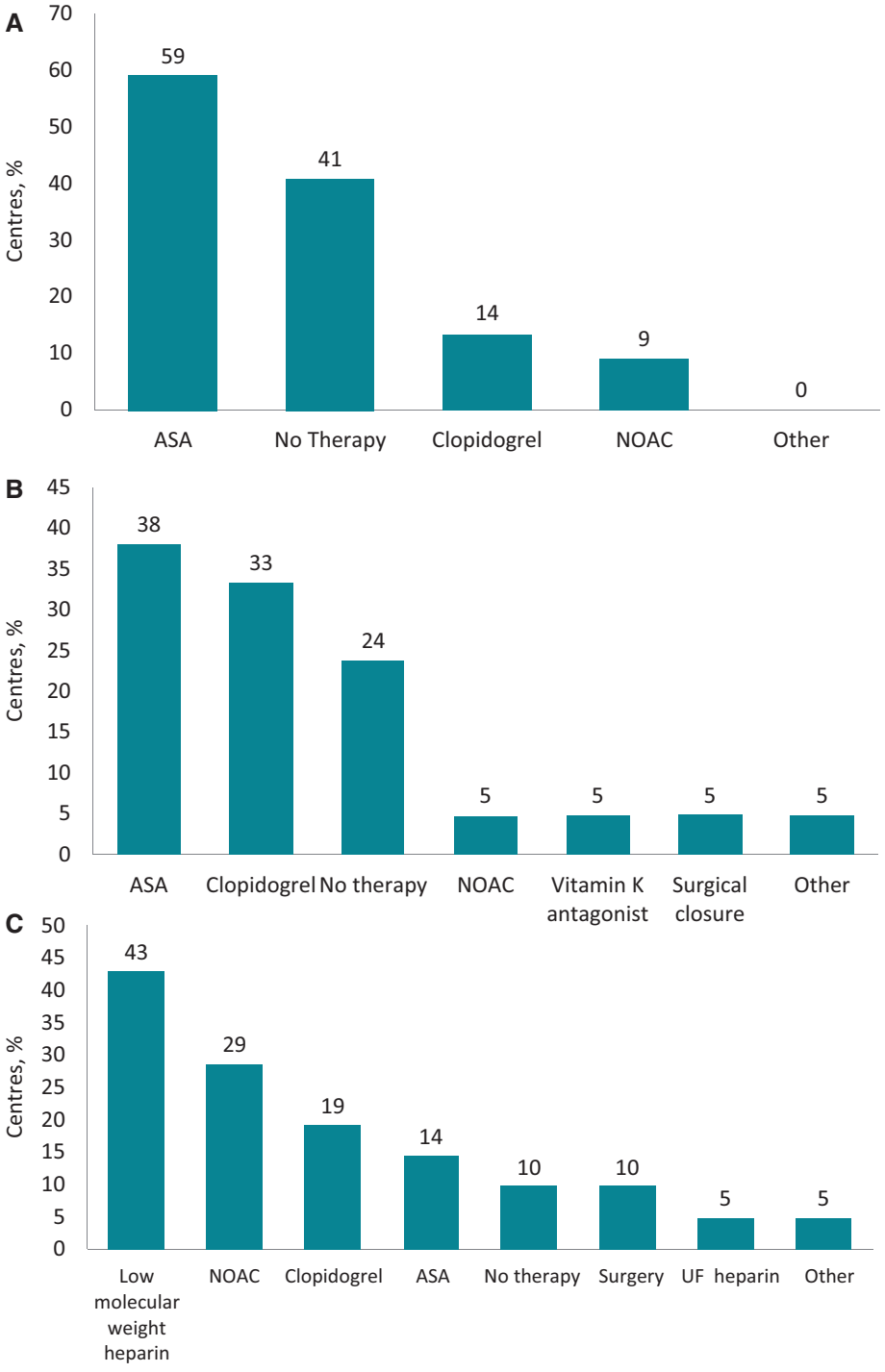

Figure 2 The predominant oral anticoagulation protocol in the long-term phase (> 6 months) post endocardial LAAO implantation in patients without contraindications to VKA or NOAC and no leak during follow-up transoesophageal echocardiography (A), in patients with absolute contraindications to VKA or NOAC and LAA leak > 5mm (B) or device thrombus (C) during follow-up transoesophageal echocardiography is (multiple answers). LAAO, left atrial appendage occluder; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation; VKA, vitamin K antagonist.

studies such as the WATCHMAN left atrial appendage system for embolic PROTECTion in patients with Atrial Fibrillation (PROTECT AF) study and Continued Access Protocol (CAP) registry, showed that increased operator experience was associated with a higher implantation success rate and a lower complication rate.[5]

In contrast to the previous EHRA survey, the majority of procedures were performed by an electrophysiologist rather than by an interventional cardiologist.[6] The procedure was performed in an EP or coronary angiography lab under general anaesthesia in most centres. The most widely available device were Amplatzer™ devices

followed by the Watchman™ device. Only one centre used the epicardial LARIAT device.

Indications

According to current guidelines, treatment with VKA or NOAC therapy is the therapy of choice for stroke prevention in patients with non-valvular AF and elevated risk factors for stroke based on the CHA_2DS_2-VASc score.[4] Although there are increasing observational data on the safety and efficacy LAAO implantation, evidence from randomized trials is sparse.[7] In the randomized PROTECT-AF study, the Watchman device was non-inferior to warfarin therapy for stroke prevention in patients with non-valvular AF and elevated stroke risk.[8] However, there was a significantly higher rate of adverse events in the LAAO group compared with the warfarin group. During long-term follow-up of 3.8 years, LAAO compared with warfarin was superior for both the composite endpoint of stroke, systemic embolism, and cardiovascular death, as well as for cardiovascular and all-cause mortality.[9] In the Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy (PREVAIL) study, LAAO was non-inferior to warfarin for ischaemic stroke prevention or serious adverse events >7 days post-procedure.[10] Although the overall number of events was very low and the differences between groups were not significant in this trial, the incidence of ischaemic events (1.9% vs. 0.7%), haemorrhagic stroke (0.4% vs. 0%), death (2.6% vs. 2.2%), and systemic embolism (0.4% vs. 0.0%) were higher in the LAAO group than in the warfarin group.

There are no randomized data on safety and efficacy of LAAO in patients with contraindications to OAC. Despite the lack of data, the current European Society of Cardiology Guidelines state that 'LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause)' (IIb, LOE B).[4]

Although it is recommended that patients should be maintained on OAC for a limited period of time post-LAAO, an absolute contraindication to NOAC was the most common indication for LAAO in this survey. The second and third most common indications were a history of bleeding on NOAC and high bleeding risk. Although these indications are in line with the current guidelines, there is still limited scientific evidence (and no evidence from randomized trials) supporting this strategy. This strategy is somehow controversial since life-long antiplatelet therapy is recommended following LAAO implantation. In the Apixaban VErsus acetylsalicylic acid to Reduce the Risk Of Embolic Stroke (AVERROES) trial, patients unsuitable to OAC therapy were randomized to apixaban or aspirin.[11] Apixaban reduced the risk of stroke or systemic embolism without increasing the risk of major bleeding (including gastrointestinal bleeding) or intracranial haemorrhage. Half the corresponding centres considered low bleeding risk a contraindication for LAAO. This is of interest, since in the randomized trials comparing LAAO with VKA, only patients eligible for VKA therapy were included.

The predominant reason for not implanting or limiting the implantation of LAAO was insufficient or controversial efficacy data compared with NOAC. This underscores the need for more data on these devices. [7] A randomized trial comparing LAAO with NOAC is on the way (Eudra CT-Nr.: 2017-000058-21) Costs were only an issue in every fourth centre.

Anticoagulation

In the PROTECT AF and in the PREVAIL trial, warfarin and aspirin therapy were initially administered post-implantation, followed by a limited time period of aspirin and clopidogrel therapy for 6 months. During long-term, aspirin monotherapy was administered in all patients without leak and thrombus. However, different anticoagulation strategies have been described in observational studies such as NOAC therapy, aspirin monotherapy, or no therapy at all.

In this survey, the post-procedural anticoagulation strategies were very heterogeneous between centres. Similar to the indications, the most commonly used OAC strategies were not supported by randomized trials. In patients without contraindications as well as in patients with absolute contraindications to VKA or NOAC and no leak during follow-up, the most common anticoagulation strategy was DAT for a limited period (e.g. 6 weeks to 6 months), followed by antiplatelet monotherapy. This is worth mentioning since DAT has a higher bleeding risk than VKA or NOAC therapy. Less than 10% of all centres used a strategy similar to the PROTECT AF and PREVAIL trial. In patients with absolute contraindications to OAC less than 5% did not prescribe any OAC or antiplatelet therapy at all.

In the long-term phase (>6 months after ablation), the predominant strategy was to prescribe aspirin or clopidogrel monotherapy. Interestingly, 41% of centres would prescribe no therapy at all in patients without contraindications to OAC. In patients with absolute contraindications to OAC and no leak during follow-up, the majority of centres would prescribe no therapy at all.

Management of left atrial appendage thrombus or significant leaks

Device thrombus formation or significant peri-device leaks (>5 mm) may occur during follow-up. In the PROTECT AF study, device-associated thrombus was observed in 4.2% of all successfully implanted patients.[5] In this survey, management of device thrombi in patients with absolute contraindications to OAC was very heterogeneous and included aspirin, clopidogrel, OAC, low molecular weight heparin, surgery, unfractionated heparin, or no therapy. The results of this *EP Wire* highlight the challenge of the management of these patients which may be a result of the lack of scientific data.

Conclusions

This *EP Wire* found that the most common indications for LAAO is stroke prevention in patients at high thrombo-embolic risk and absolute contraindications to OAC or a history of bleeding. Early- and long-term post-implantation anticoagulation strategies in patients with and without device thrombus were very heterogeneous between centres with most strategies not being supported by the randomized clinical trials.

Acknowledgements

The production of this *EP Wire* document is under the responsibility of the Scientific Initiative Committee of the European Heart Rhythm

Association: Nikolaos Dagres (Chair), Tatjana S. Potpara (Co-chair), Serge Boveda, Jian Chen, Jean Claude Deharo, Dan Dobreanu, Stefano Fumagalli, Kristina H. Haugaa, Torben Bjerregaard Larsen, Radosław Lenarczyk, Antonio Madrid, Elena Sciaraffia, Milos Taborsky, and Roland Tilz. Document reviewer for EP-Europace: Irina Savelieva (St George's University of London, London, UK). The authors acknowledge the EHRA Research Network centres participating in this EP Wire. A list of the Research Network can be found on the EHRA website.

Conflict of interest: none declared.

References

1. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *J Am Coll Cardiol* 1995; **25**:452–9.
2. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C *et al.* EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace* 2014;**16**:1397–416.
3. Pison L, Potpara TS, Chen J, Larsen TB, Bongiorni MG, Blomstrom-Lundqvist C *et al.* Left atrial appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey. *Europace* 2015;**17**: 642–6.
4. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
5. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the watchman left atrial appendage system for embolic Protection in Patients with AF (PROTECT AF) clinical trial and the continued access registry. *Circulation* 2011;**123**:417–24.
6. Lip GYH, Dagres N, Proclemer A, Svendsen JH, Pison L, Blomstrom-Lundqvist C *et al.* Left atrial appendage occlusion for stroke prevention in atrial fibrillation in Europe: results of the European Heart Rhythm Association survey. *Europace* 2012;**15**:141–3.
7. Tzikas A, Holmes DR Jr, Gafoor S, Ruiz CE, Blomström-Lundqvist C, Diener HC *et al.* Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. *Europace* 2017;**19**:4–15.
8. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M *et al.* Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients withatrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–42.
9. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P *et al.* Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation. *JAMA* 2014;**312**:1988.
10. Holmes DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK *et al.* Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**:1–12.
11. Connolly SJ, Eikelboom J, Joyner C, Diener H-C, Hart R, Golitsyn S *et al.* Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–17.